The Dapivirine and Levonorgestrel MPT Ring: Understanding the Levonorgestrel Binding Reaction with Silicone Elastomer

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Innovative 3D Printed Intravaginal Rings: Reengineering Multipurpose Intravaginal Rings for Prevention of HIV and Unintended Pregnancy

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Background: Over 50% of HIV infected individuals are women, and ~50% of all pregnancies are unplanned. Therefore, there is a critical need to promote convenient, female-controlled methods of multipurpose prevention and delivery strategies. Intravaginal rings (IVRs) are well tolerated by women, are efficacious for contraception and hormone replacement therapy, and have high patient compliance. However, developing effective multipurpose IVRs is challenging due to the complexity of current engineering processes and differences in drug properties and release rates, thus mandating drug-specific customized IVR designs. Our goal is to address these limitations by revolutionizing the engineering process of IVRs using a state-of-the-art 3D printing process known as the continuous liquid interface production (CLIP™). This versatile technology implements digital computer aided design combined with digital light synthesis to rapidly engineer geometrically complex 3D objects.
Methods: IVRs with complex geometries were fabricated with the CLIP technology. *In vitro* release of 3 antiretroviral drugs (ARVs) and 4 contraceptives was assessed with 3D printed IVRs. *In vitro* and *in vivo* safety, including the effect on the vaginal microbiome was assessed with mouse size IVRs.
Results: IVRs with a range of designs, surface area, mechanical properties, and sizes were fabricated using the CLIP technology. We have demonstrated the ability to fine-tune release kinetics of contraceptive drugs (β-estradiol, progesterone, EE, and ENG) and ARVs (DTG, TDF, and DLV). We have demonstrated the ability to co-formulate multiple drugs in a single IVR with a range of designs. 3D CLIP IVRs were shown to be safe *in vitro* and *in vivo*, including limited impact on transplanted human vaginal microbiomes that colonized vaginal mucosal cultures.
Conclusions: 3D printing allows rapid manufacturing of custom-sized IVRs and IVRs that can integrate multiple drugs providing a novel cost-effective platform for the fine-tuned vaginal release of drugs.

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The Dapivirine and Levonorgestrel MPT Ring: Understanding the Levonorgestrel Binding Reaction with Silicone Elastomer

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Background: As part of ongoing efforts to refine and optimize a MPT vaginal ring (VR) releasing dapivirine (DPV) and levonorgestrel (LNG), we previously reported that LNG can irreversibly bind to addition cure silicone elastomers, with the extent of reaction dependent upon the cure time, cure temperature and the LNG particle size properties. Here, we further explore the LNG binding phenomenon using three custom silicone elastomers.
Methods: PROTO BSL 086 and Silbione® 4370 were supplied by Bluestar Silicone (York, USA). PROTO ESL 008 was provided by Elkem Silicones (Leverkusen, Germany). Micronised LNG was added and mixed into both parts A and B of each silicone system. Matrix-type, silicone elastomer VRs (~8 g weight, 57 mm overall diameter, 7.8 mm cross-sectional diameter) containing either 32 or 320 mg LNG with were manufactured by injection molding. The BSL 086 VRs were cured at 70˚C/1 min using pre-chilled PROTO BSL 086 materials. The ESL 008 and 4370 VRs were cured at 105˚C/1 min and 140˚C/2 min, respectively. Percentage LNG recovery was quantified by HPLC following acetone extraction. VRs were also exposed to various additional heat treatments, followed by LNG extraction and quantification. Acetone extracts and extracted rings were analysed by ^{1}H-NMR.
Results: Low LNG assay indicating LNG reaction was also observed with the custom silicone elastomers. Mean LNG recoveries from 32 and 320 mg rings were 70 and 99% (BSL 086), 55 and 91% (ESL 008) and 0.2 and 75 % for 4370 VRs, respectively. Additional LNG binding in the VRs was observed upon further heat treatment, giving insights into potential further losses of LNG during ring storage stability. ^{1}H-NMR data provided direct evidence for the reaction product between the ethynyl group of LNG and silicone.
Conclusions: As with previously tested commercially available silicone elastomers, LNG binding was also observed with custom silicone elastomer materials. LNG recovery values were much higher with a 320 mg initial LNG loading compared to a 32 mg loading.